SYSTEMATIC REVIEW/META-ANALYSIS

Effectiveness of Balanced Electrolyte Solution vs Normal Saline in the Resuscitation of Adult Patients with Diabetic Ketoacidosis: An Updated Systematic Review and Meta-analysis

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Abstract

Aim and background: Fluid resuscitation is the first-line treatment for patients with diabetic ketoacidosis (DKA). However, the optimal choice of resuscitative fluid remains controversial. This study aims to evaluate the impact of balanced electrolyte solution (BES) compared to 0.9% sodium chloride (NS) on various physiological and clinical outcomes in adult DKA patients.

Materials and methods: An extensive search of electronic databases, including Embase, PubMed, Cochrane Library, Web of Science, and Google Scholar, was conducted to select studies that directly compared BES and NS in adult DKA patients. This systematic review and meta-analysis included nine studies, comprising both randomized controlled trials and retrospective studies. Combined estimates were expressed as mean differences (MDs) with 95% confidence intervals (CIs). The primary outcomes were time to resolution of DKA and length of hospital stay. The secondary outcomes were post-resuscitation chloride and bicarbonate levels and adverse events.

Results: No significant difference was observed between BES and NS in the time to DKA resolution (MD: –1.63; 95% CI: –7.66–4.41; $p = 0.60$) or length of hospital stay (MD: –0.07; 95% CI: –0.44–0.31; $p = 0.73$). However, BES resulted in significantly higher post-resuscitation bicarbonate levels (MD: 1.63; 95% CI: 0.86–2.39; $p < 0.001$) and lower post-resuscitation chloride levels (MD: –2.37; 95% CI: –3.56 to –1.19; $p < 0.001$).

Conclusion: The use of BES is associated with improved post-resuscitation electrolyte balance and preventing hyperchloremic metabolic acidosis in DKA patients. While BES may offer some biochemical advantages, both BES and NS are safe for treating DKA.

Keywords: Balanced electrolyte solution, Diabetic ketoacidosis, Fluid resuscitation, Metabolic acidosis, Normal saline, Systematic review and meta-analysis.

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Highlights

- This systematic review and meta-analysis found no significant differences in time to diabetic ketoacidosis (DKA) resolution or length of hospital stay between balanced electrolyte solutions (BES) with 0.9% sodium chloride (NS) in adult patients with DKA.
- Balanced electrolyte solutions were associated with better post-resuscitation electrolyte balance compared to NS.

Introduction

Diabetic ketoacidosis is marked by uncontrolled high blood sugar, metabolic acidosis, and increased ketone levels in the body. The incidence of DKA varies significantly across different regions, ranging from 0 to 56 cases per 1000 person-years.[1,2] Mortality rates for DKA as an initial diagnosis of diabetes mellitus (DM) vary globally, ranging from 0.15 to 0.35% among young individuals, whereas in developing countries like India and Bangladesh, studies report rates between 3.4 and 13.4%. Key causes of DKA-related deaths in these regions include cerebral edema, sepsis, and renal failure.[3,4]

Diabetic ketoacidosis treatment focuses on addressing acidosis, elevated ketone levels, dehydration, and any electrolyte imbalances while also gradually bringing blood sugar levels back to normal.[5] The primary strategies for managing DKA include fluid resuscitation and maintenance, insulin therapy, electrolyte replacement, addressing the underlying cause or removing the precipitating factor, and providing supportive care.[1]

In addition to insulin therapy, administering intravenous fluids (IVF) to correct the dehydration is crucial for the acute management of DKA.[6–8] Prompt fluid resuscitation is essential for correcting

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SHOUT
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Table 1: Search strings utilized across the different assessed databases

Database	*Search string*
PubMed	(("Diabetic ketoacidosis"[MeSH Terms]) OR "DKA" OR "diabetic coma") AND (("fluid therapy"[MeSH Terms]) OR "Intravenous Fluids" OR "IV Fluids" OR "hydration" OR "rehydration") AND (("Outcome assessment (healthcare)"[MeSH Terms]) OR "patient outcome assessment"[MeSH Terms] OR "treatment outcome" OR "clinical outcomes" OR "resolution time") AND english[lang] AND humans [Mesh].
Cochrane Library	("Diabetic Ketoacidosis":ti,ab,kw OR "DKA":ti,ab,kw OR "diabetic coma":ti,ab,kw) AND ("fluid therapy":ti,ab,kw OR "intravenous fluids":ti,ab,kw OR "IV fluids":ti,ab,kw OR "hydration":ti,ab,kw OR "rehydration":ti,ab,kw) AND ("patient outcome":ti,ab,kw OR "treatment outcome":ti,ab,kw OR "clinical outcomes":ti,ab,kw OR "resolution time":ti,ab,kw) AND "humans":kw
Embase	('diabetic ketoacidosis'/exp OR 'DKA':ab,ti OR 'diabetic coma':ab,ti) AND ('fluid therapy'/exp OR 'intravenous fluids':ab,ti OR 'iv fluids':ab,ti OR 'hydration':ab,ti OR 'rehydration':ab,ti) AND ('patient outcome':ab,ti OR 'treatment outcome':ab,ti OR 'clinical outcomes':ab,ti OR 'resolution time':ab,ti) AND [humans]/lim AND [english]/lim
Google Scholar	("Diabetic ketoacidosis" OR "DKA" OR "diabetic coma") AND ("fluid therapy" OR "intravenous fluids" OR "IV fluids" OR "hydration" OR "rehydration") AND ("patient outcome" OR "treatment outcome" OR "clinical outcomes" OR "resolution time")
Web of Science	(TS = ("Diabetic ketoacidosis") OR TS = ("DKA") OR TS = ("diabetic coma")) AND (TS = ("fluid therapy") OR TS = ("intravenous fluids") OR TS = ("IV fluids") OR TS = ("hydration") OR TS = ("rehydration")) AND (TS = ("patient outcome") OR TS = ("treatment outcome") OR TS = ("clinical outcomes") OR TS = ("resolution time")) AND LANGUAGE: (English) AND DOCUMENT TYPES: (Article OR Review)

hypovolemia, eliminating ketones, and restoring tissue perfusion. This also improves glycemic control and insulin sensitivity and reduces counter-regulatory hormone levels.[9]

The American Diabetes Association (ADA) guidelines for DKA recommend aggressive fluid resuscitation with 0.9% sodium chloride/normal saline (NS) until serum glucose reaches ~200 mg/dL, and then fluid resuscitation is continued with dextrose-containing solutions until acidosis is resolved and the anion gap is closed. In spite of frequent use of NS, it has certain limitations, such as a pH of 5.5 and high chloride content.[10] Normal saline has a strong ion difference (SID) of zero and a chloride concentration of 154 mmoL/L, which is much higher than the chloride concentration in human plasma (94–111 mmoL/L).[11–14] This difference can possibly lead to hyperchloremic metabolic acidosis when given in large amounts.[11–14] There is evidence indicating that administering large volumes of NS can lead to hyperchloremia, hypernatremia, acute kidney injury (AKI), non-anion gap metabolic acidosis, and higher mortality.[15–20] These issues might contribute to longer hospitalizations due to worsening acidosis in DKA.

The chloride concentrations in BES, like Plasmalyte-A (PL-A) and Ringer lactate, are almost equivalent to human plasma and hence unlikely to cause metabolic acidosis.[11–14] Balanced electrolyte solution achieves a near-physiological SID (~40 mEq/L) by substituting some of the chloride with bicarbonate, acetate, lactate, and gluconate.[15] Due to the high chloride content in NS potentially causing adverse effects, BES are increasingly used as alternatives.[21] Consequently, treating DKA with BES instead of NS may result in an effective and safe resolution of the dehydration and electrolyte imbalances.[20,22–24]

Currently published systematic reviews and meta-analyses comparing BES and NS have incorporated data from pediatric patients, highlighting a gap in adult-specific data.[15,24,25] The availability of recent evidence further prompted the conduct of an updated meta-analysis.[26,27] Given the extensive use of IVF therapy globally, even the small differences in the choice of fluid selection may have a significant impact on clinical outcomes. Therefore, this systematic review and meta-analysis was carried out to investigate and compare the efficacy of NS and BES in the resuscitation of adult DKA patients.

Materials and Methods

Study Design

This meta-analysis was performed according to the updated PRISMA guidelines statement.[28] The protocol of this meta-analysis has been registered in the PROSPERO (ID: CRD42024565074).

Study Objectives

Primary objectives were to compare the time to resolution of DKA and length of hospital stay between patients receiving NS and those receiving BES during resuscitation. Secondary objectives were to compare post-resuscitation chloride and bicarbonate levels between NS and BES in patients treated for DKA and to assess the incidence of adverse events (AEs), including hypokalemia, hyperkalemia, AKI, and mortality.

Search Strategies

The search strategy was designed to incorporate both free text terms and MeSH (Medical Subject Headings) keywords, utilizing Boolean operators to refine the search results across the Cochrane Library, PubMed, Embase, Web of Science, and Google Scholar, from the date of inception till May 14, 2024 (Table 1). The research included studies comparing NS with BES in the treatment of hospitalized adults with DKA.

Study Selection and Data Extraction

We utilized the Covidence online platform (www.covidence.org) for screening purposes. Initially, we aggregated search findings from all sources and eliminated duplicate entries. Two independent reviewers conducted screening concurrently using a two-phase approach. In the first phase, titles and abstracts were assessed, with potentially relevant citations progressing to the second phase. Eligibility of trials was assessed independently, with reasons for exclusion documented. During phase II, both reviewers independently evaluated full texts, resolving any discrepancies through consensus. We also manually screened references from previously published original articles, meta-analyses, and reviews. Moreover, a manual search was conducted of the references cited in the included articles to ensure comprehensive coverage.

The data were obtained on the study designs, demographics of patients (age, sex), study participants (randomized and considered for analysis), method used for diagnosis of DKA, time to resolution of DKA, changes in serum chloride and bicarbonate, mortality rate, duration of hospital stay, and the number of AEs. After extracting the data, a third author reviewed the extracted information to ensure its accuracy. The included studies were tabulated as per study design, patient population, treatment, key results, and conclusion.

Eligibility Criteria

The inclusion criteria were as follows:

- Study design: Randomized controlled trials (RCTs) as well as prospective and retrospective studies (full text).
- Study population: Patients diagnosed with DKA as per the current international guidelines.[29,30]
- Medications: BES, such as Plasma-Lyte, Lactated Ringer's).
- Comparison group: NS
- Outcomes: Time to resolution of DKA resolution and length of hospital stay, post-resuscitation chloride levels, post-resuscitation bicarbonate levels, and adverse events, including hypokalemia, hyperkalemia, acute kidney injury, and mortality.
- Studies were excluded if they involved patients without DKA, did not administer NS or BES, were duplicates presenting the same patients as presented in the included study, were single-arm trials, or were case reports, case series, review articles, conference abstracts, or posters letters to the editor.

Assessment of Risk of Bias

The risk of bias (ROB) was independently evaluated by two reviewers using the "Cochrane RoB 2: a revised tool for assessing the risk of bias in RCT."[31] Any disagreements that occurred throughout the course were resolved via discussion.

Statistical Analyses

To compare NS with BES, a pairwise meta-analysis was performed using STATA 10. For each of the outcomes of interest, a meta-analysis was performed. Dichotomous outcomes were used to generate log odds (logOR) with 95% confidence intervals (CIs) from the included studies. The I^2 statistic was used to evaluate heterogeneity. Heterogeneity was deemed significant when the I^2 statistic was >50%. Based on *Q*-statistics, if I^2 was >50% and/or $p < 0.05$, the pooled logORs were deemed heterogenous. Statistical significance was considered at $p \leq 0.05$.

Results

Search Results and Study Selection

A total of 416 articles were found in the systematic search of the databases, and 47 articles were excluded because of duplication after manual screening. Moreover, 58 articles were excluded due to unavailability of full-text and another 42 articles could not be retrieved. Another 259 articles were excluded due to various reasons, resulting in the inclusion of nine studies (Fig. 1).[2,10,20,26,27,32–35]

Study Characteristics

A total of nine studies meeting the inclusion and exclusion criteria were included with a total patient population of 937, involving 443 patients in the BES group and 494 in the NS group.[2,10,20,26,27,32–35] Of nine studies, seven were RCTs[2,20,26,27,32,34,35] while the remaining two were retrospective in nature.[10,33] Of two retrospective studies,

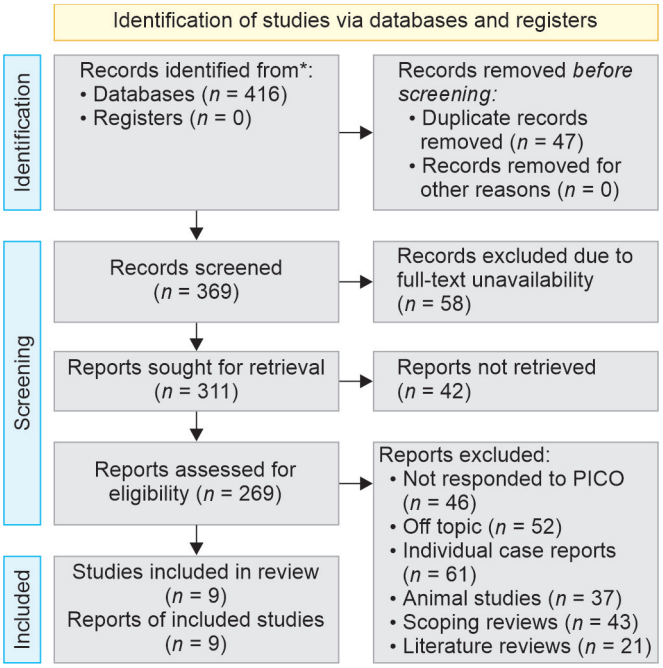

Identification of studies via databases and registers
Identification
Records identified from*:
• Databases (n = 416)
• Registers (n = 0)
Records removed before screening:
• Duplicate records removed (n = 47)
• Records removed for other reasons (n = 0)
Screening
Records screened (n = 369)
Records excluded due to full-text unavailability (n = 58)
Reports sought for retrieval (n = 311)
Reports not retrieved (n = 42)
Reports assessed for eligibility (n = 269)
Reports excluded:
• Not responded to PICO (n = 46)
• Off topic (n = 52)
• Individual case reports (n = 61)
• Animal studies (n = 37)
• Scoping reviews (n = 43)
• Literature reviews (n = 21)
Included
Studies included in review (n = 9)
Reports of included studies (n = 9)

Fig. 1: PRISMA flow diagram showing the literature search process

both were single centric,[10,33] while among RCTs, four were single centric,[2,27,32,34] two took place at two different centers,[20,26] and one was conducted at seven centers.[35] Among RCTs, one was single blind,[34] two were double blind,[2,20] one was triple blind,[27] and three were open label.[26,32,35] All the studies included patients aged ≥18 years,[2,10,20,27,32–34] except two studies that included patients aged ≥16 years.[26,35] Of nine studies, four compared RL with NS,[10,20,27,34] two compared PL-A with NS,[2,33] two compared PL-148 with NS[26,35] and one compared RL/PL-A with NS.[32] Of all the included studies, only one was a subgroup analysis of two RCTs.[32] The summary of the included studies is depicted in Table 2.

Primary Outcomes

Time to DKA Resolution

The analysis of four eligible studies revealed no difference between BES and NS in mean time to DKA resolution (mean difference: –3.37 h; 95% CI: –8.61–1.87; $p = 0.21$).[20,27,32,35] However, significant heterogeneity was observed between the studies ($I^2 = 74.83\%$, $p < 0.001$). Exclusion of the study by Self et al. from the analysis[32] decreased the heterogeneity to a non-significant level ($I^2 = 66.65\%$, $p = 0.05$), and the difference between BES and NS in mean time to DKA resolution remained non-significant (mean difference: –1.63 h; 95% CI: –7.66–4.41; $p = 0.60$) (Fig. 2).

Length of Hospital Stay

No difference in mean length of hospital stay was observed between BES and NS from the analysis of five eligible studies (mean difference: –0.07; 95% CI: –0.44–0.31; $p = 0.73$),[10,20,26,27,32,35] and there was no significant heterogeneity between the studies ($I^2 = 0.00\%$, $p = 0.38$) (Fig. 3).

Secondary Outcomes

Post-resuscitation Chloride Levels

The mean post-resuscitation chloride levels were significantly higher in the NS group compared to the BES group (mean difference:

Table 2: Summary of the included studies

Author ID	*Study design*	*Population characteristics*	*Groups assessed*	*Key findings*	*Overall conclusion drawn*
Yan et al. (2023)[27]	Parallel-arm, triple-blind pilot RCT	Adults with DKA, recruited from a Canadian ED	Randomized 1:1 to receive either RL or NS	Recruitment rate exceeded target (52/60, 86.7%). Median time to DKA resolution: 15.7 hours (RL) vs 12.7 hours (NS). No blinding breaks or loss to follow-up.	RL did not lead to a significant reduction in the time needed for DKA resolution compared to NS, despite achieving the recruitment targets successfully.
Attokaran et al. (2023)[26]	Prespecified nested cohort study within a RCT	Patients presenting to the ED with DKA during a fixed recruitment period	NS (n = 38) vs Plasmalyte-148 (PL, n = 46)	No significant difference in ICU admission rates after adjustment for pH and diabetes type (p = 0.71).	PL showed no significant difference compared to NS in decreasing ICU admission rates for DKA patients in the ED.
Carrillo et al. (2022)[10]	Retrospective cohort study	Adults aged ≥18 years admitted to the University of New Mexico Hospital	RL (n = 143) vs NS (n = 183)	Hyperchloremia occurred more frequently with NS than RL (74.4 vs 64.2%; p = 0.05). Mean maximum serum chloride was higher with NS (115.7 vs 113.7 mmol/L; p = 0.004). Incidence of hypernatremia was higher with NS (18.3 vs 9.3%; p = 0.02). There was significantly greater reduction in the serum creatinine in RL group (-0.15 vs -0.04 mg/dL; p = 0.002) at 48 h.	RL resulted in a notable decrease in hyperchloremia occurrence compared to NS. Improvement in serum creatinine levels was more pronounced with RL than NS after 48 h.
Ramanan et al. (2021)[35]	Cluster, crossover, open-label, randomized, controlled Phase 2 trial	Patients 16 years of age and over presenting to the emergency department or ICU	Plasma-Lyte-148 (PL, n = 48) vs NS (n = 42)	DKA resolution at 48 h occurred in 96% (PL) and 86% (NS) of patients; (p = 0.111). At 24 h, DKA resolution occurred in 69% (PL) and 36% (NS) of patients (p = 0.002). Median ICU and hospital stay were 49 vs 55 h and 81 vs 98 h in the PL and NS groups.	PL, in contrast to NS, could result in quicker correction of metabolic acidosis in individuals with diabetic ketoacidosis without exacerbating ketosis.
Self et al. (2020)[32]	Subgroup analysis of cluster randomized clinical trials	172 adults with DKA at an academic medical center in the US	Balanced crystalloids (RL or PL-A) vs NS	Balanced crystalloids group had shorter time to DKA resolution (median: 13.0 h) compared to saline group (median: 16.9 h, p = 0.004) and shorter time to insulin infusion discontinuation (p = 0.03).	Balanced crystalloid solutions, in contrast to NS, led to quicker resolution of DKA and cessation of insulin infusion.
Oliver et al. (2018)[33]	Retrospective analysis	DKA patients treated at a large academic medical center over 2 years	PL group vs NS group based on predominant fluid received	Similar time to DKA resolution (p = 0.508); PL group had greater pH rise and lower anion gap in 6–12 h.	PL may provide advantages in comparison to NS, as indicated by a more significant increase in pH and a reduced anion gap during the resuscitation of DKA.
Aditianingsih et al. (2017)[34]	Prospective, randomized, single blind controlled trial	Patients aged 18–65 years and admitted in ED of Cipto Mangunkusumo Hospital, Indonesia	RL group (n = 15) vs NS group (n = 15)	SID was significantly greater with BES than NS group (p < 0.05). At 18 hours, SBE was significantly higher with BES than NS group (–4.88 ± 5.69 vs –9.68 ± 5.64; p = 0.009). Also at 24 h (–3.99 ± 4.27 vs –8.7 ± 5.35; p = 0.023), and 48 h (–4.06 ± 4.11 vs –7.01 ± 5.46; p = 0.009), it was significantly higher with BES compared to NS group. Higher delta SBE and SID was noted with BES than NS.	Fluid resuscitation of patients with DKA using BES led to marginally higher mean actual SBE and SID compared to NS, although the difference was not statistically significant.

(Contd...)

Table 2: *(Contd...)*

Author ID	*Study design*	*Population characteristics*	*Groups assessed*	*Key findings*	*Overall conclusion drawn*
Van Zyl et al. (2011)[20]	Parallel double-blind RCT	Adults >18 years with DKA, venous pH >6.9 and <7.2, blood glucose >13 mmol/l, urine ketones 52+, alert, <1l pre-enrolment resuscitation fluid	29 patients with 0.9% NS, 28 with RL	No significant difference in pH normalization time (HR 1.863, $p = 0.076$). Median time to pH 7.32: 683 min (NS) vs 540 min (RL), $p = 0.251$. Time to reduce glucose to 14 mmol/l longer in RL group, $p = 0.044$. Time to DKA resolution similar.	RL did not show any advantage over NS in speeding up pH normalization among patients with DKA.
Mahler et al. (2011)[2]	Prospective, randomized, double-blind study	DKA patients 18–65 years at Louisiana State University Health Sciences Center-Shreveport	NS group vs BES (Plasma-Lyte A) group	BES group had lower mean post-resuscitation chloride ($p \leq 0.001$) and higher bicarbonate ($p = 0.020$).	Bicarbonate and chloride profiles might be more advantageous with BES compared to NS during resuscitation for DKA.

BES, balanced electrolyte solution; DKA, diabetic ketoacidosis; ED, emergency department; NS, normal saline; PL, plasmalyte; RL, ringer's lactate; SBE, standard base excess; SID, strong ion difference

–2.37; 95% CI: –3.56 to –1.19; $p < 0.001$). There was no significant heterogeneity between the six eligible studies ($I^2 = 54.71\%$, $p = 0.06$) (Fig. 4). Similarly, the mean post-resuscitation bicarbonate levels were significantly higher in BES compared to NS (mean difference: 1.63; 95% CI: 0.86–2.39; $p < 0.001$). There was no significant heterogeneity between the included studies ($I^2 = 15.77\%$, $p = 0.42$) (Fig. 5).[2,10,20,26,32,35]

Hypokalemia, Hyperkalemia, and Acute Kidney Injury

The incidence rate of hypokalemia showed no significant difference between BES and NS (3 studies, mean difference: 0.16; 95% CI: –0.92–1.25; $p = 0.77$) with no significant heterogeneity between the studies ($I^2 = 66.38\%$, $p = 0.05$).[27,32,35] No significant difference was observed in the incidence of hyperkalemia between BES and NS (2 studies, mean difference: –0.24; 95% CI: –2.41–1.93; $p = 0.83$, $I^2 = 88.20\%$, $p < 0.001$) (Figs 6 to 9).[27,32] Similarly, there was no increased incidence of AKI in NS compared to BES (4 studies, mean difference: –0.24; 95% CI: –1.01–0.54; $p = 0.55$, $I^2 = 0.00\%$, $p = 0.86$).[10,27,32,34]

Mortality

No significant difference was observed between BES and NS groups in the incidence of mortality (7 studies, mean difference: 0.34; 95% CI: –0.50–1.18; $p = 0.43$, $I^2 = 0.00\%$, $p = 0.98$) (Fig. 10).[10,20,26,32–35]

Risk of Bias

The approach for statistical analysis was intention-to-treat in six studies[2,20,27,32,34,35] and per-protocol in three studies.[10,26,33] Overall, the included studies had variable ROB ranging from low to high risk. The ROB was low in five studies[2,20,26,27,34] and high in four studies (Fig. 10).[10,32,33,35]

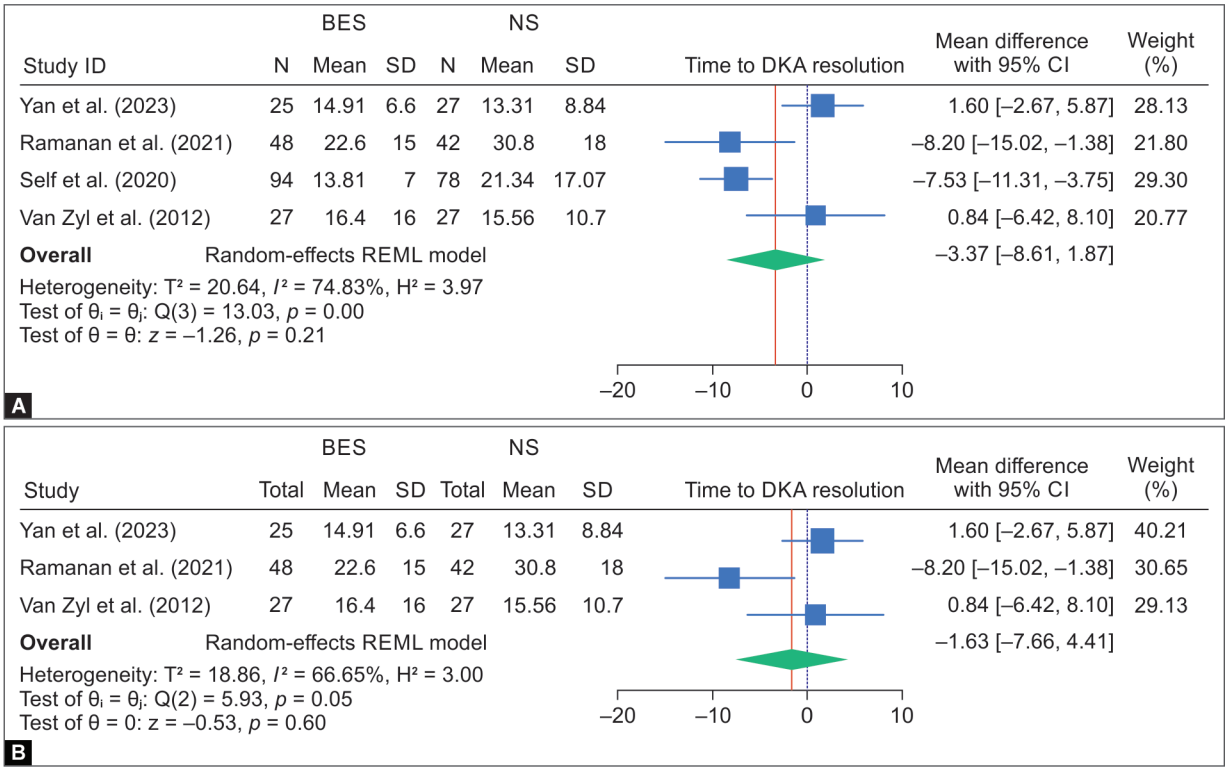
Discussion

This updated systematic review and meta-analysis encompassed nine studies, including seven RCTs[2,20,26,27,32,34,35] and two retrospective studies,[10,33] examining the effects of NS vs BES in DKA patients. For time to DKA resolution or duration of hospital stay, we observed no significant differences between the NS and BES groups. However, the patients receiving NS had significantly higher post-resuscitation chloride levels, while patients receiving BES had significantly higher post-resuscitation bicarbonate levels. Adverse events were infrequent, with comparable rates of hypokalemia, hyperkalemia, AKI, and mortality between NS and BES groups.

In pooled analyses, there was no significant difference in the time to DKA resolution between NS and BES. These findings are consistent with recent systematic reviews and meta-analyses conducted by Liu et al.[24] and Tamzil et al.,[15] which reported comparable results. However, an earlier systematic review and meta-analysis by Alghamdi et al.[25] suggested a longer DKA resolution time with NS, while Catahay et al.[36] indicated faster DKA resolution with BES.

The time to resolve DKA is critical, as quicker recovery often leads to shorter ICU stays and earlier discharge. Contrasting with Alghamdi et al.'s findings of longer stays with NS,[25] our pooled analysis found no significant difference in length of hospital stay between the NS and BES interventions. Although the combined differences in DKA resolution time and length of hospital stay were minor, they remain important for patient outcomes and healthcare resource management.

Post-resuscitation electrolyte concentrations are important indicators of illness severity and the need for continued ICU care.


BES
NS
Study ID N Mean SD N Mean SD
Time to DKA resolution
Mean difference with 95% CI
Weight (%)
Yan et al. (2023) 25 14.91 6.6 27 13.31 8.84 1.60 [–2.67, 5.87] 28.13
Ramanan et al. (2021) 48 22.6 15 42 30.8 18 –8.20 [–15.02, –1.38] 21.80
Self et al. (2020) 94 13.81 7 78 21.34 17.07 –7.53 [–11.31, –3.75] 29.30
Van Zyl et al. (2012) 27 16.4 16 27 15.56 10.7 0.84 [–6.42, 8.10] 20.77
Overall Random-effects REML model –3.37 [–8.61, 1.87]
Heterogeneity: T² = 20.64, I² = 74.83%, H² = 3.97
Test of θi = θj: Q(3) = 13.03, p = 0.00
Test of θ = θ: z = –1.26, p = 0.21
–20 –10 0 10
A
BES
NS
Study Total Mean SD Total Mean SD
Time to DKA resolution
Mean difference with 95% CI
Weight (%)
Yan et al. (2023) 25 14.91 6.6 27 13.31 8.84 1.60 [–2.67, 5.87] 40.21
Ramanan et al. (2021) 48 22.6 15 42 30.8 18 –8.20 [–15.02, –1.38] 30.65
Van Zyl et al. (2012) 27 16.4 16 27 15.56 10.7 0.84 [–6.42, 8.10] 29.13
Overall Random-effects REML model –1.63 [–7.66, 4.41]
Heterogeneity: T² = 18.86, I² = 66.65%, H² = 3.00
Test of θi = θj: Q(2) = 5.93, p = 0.05
Test of θ = 0: z = –0.53, p = 0.60
–20 –10 0 10
B

Figs 2A and B: (A) Forest plot of time to DKA resolution; (B) Forest plot of time to DKA resolution

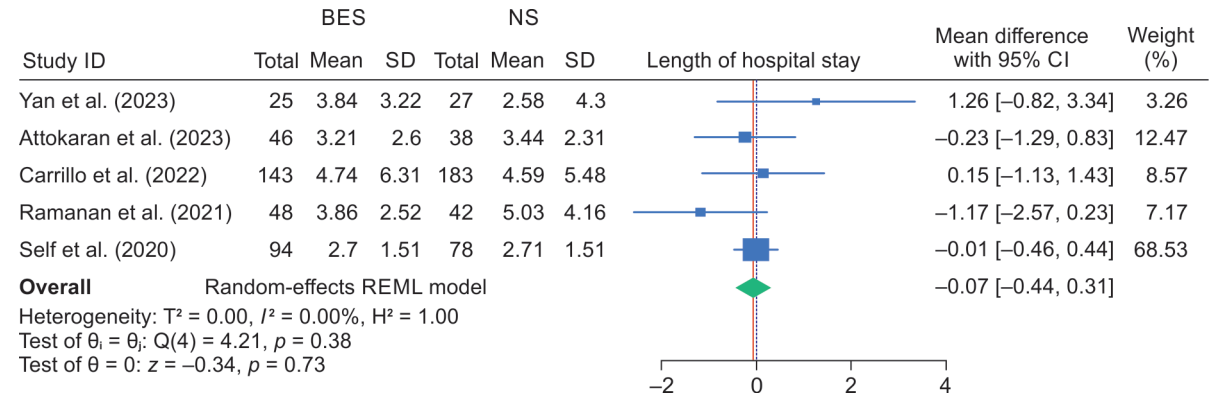


Fig. 3: Forest plot of length of hospital stay

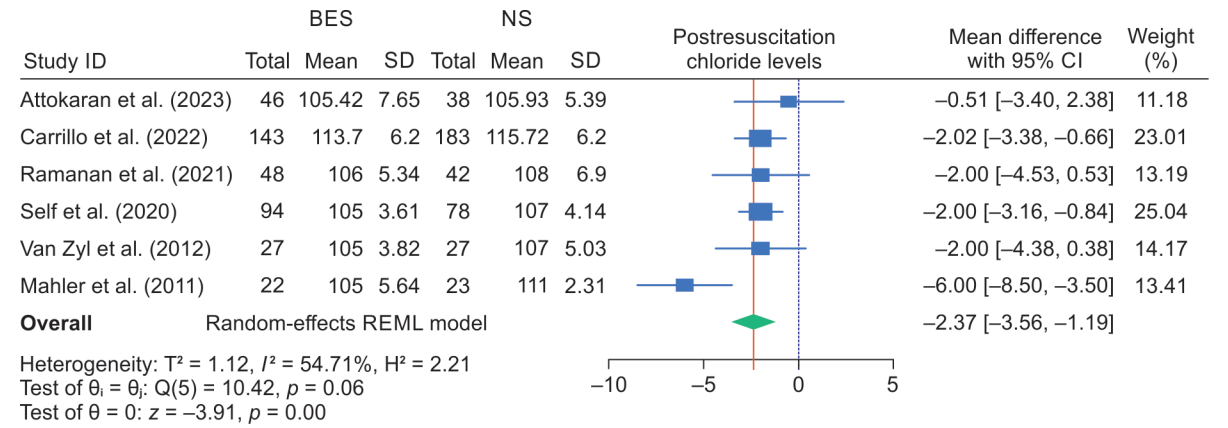


Fig. 4: Forest plot of post-resuscitation chloride levels

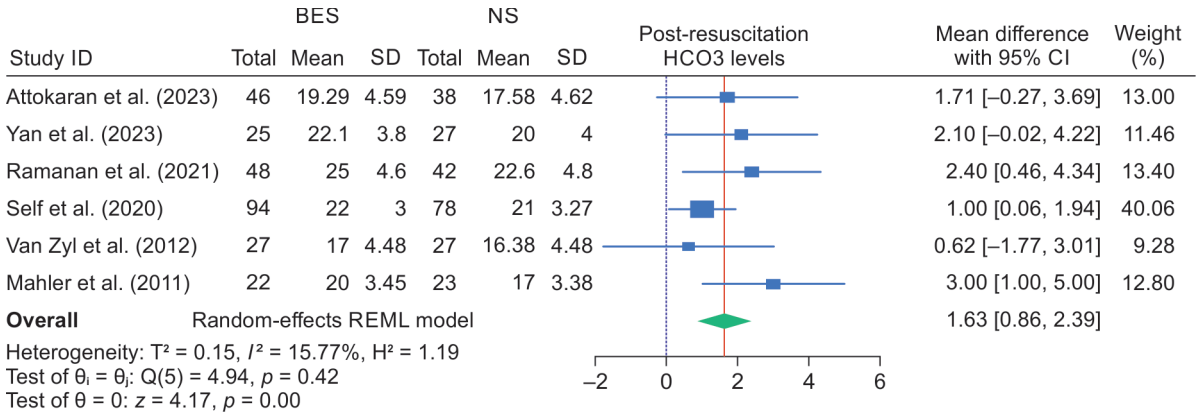


Fig. 5: Forest plot of post-resuscitation bicarbonate levels

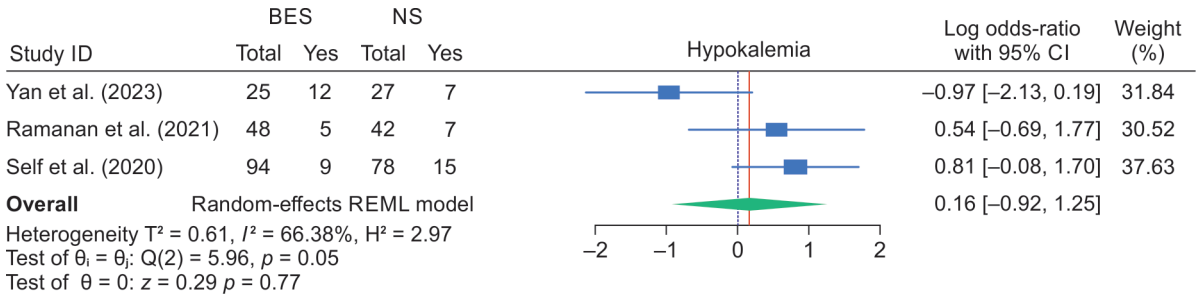

BES
NS
Study ID
Total
Yes
Total
Yes
Hypokalemia
Log odds-ratio with 95% CI
Weight (%)
Yan et al. (2023) 25 12 27 7 –0.97 [–2.13, 0.19] 31.84
Ramanan et al. (2021) 48 5 42 7 0.54 [–0.69, 1.77] 30.52
Self et al. (2020) 94 9 78 15 0.81 [–0.08, 1.70] 37.63
Overall Random-effects REML model 0.16 [–0.92, 1.25]
Heterogeneity T² = 0.61, I² = 66.38%, H² = 2.97
Test of θi = θj: Q(2) = 5.96, p = 0.05
Test of θ = 0: z = 0.29 p = 0.77
–2
–1
0
1
2

Fig. 6: Forest plot of hypokalemia

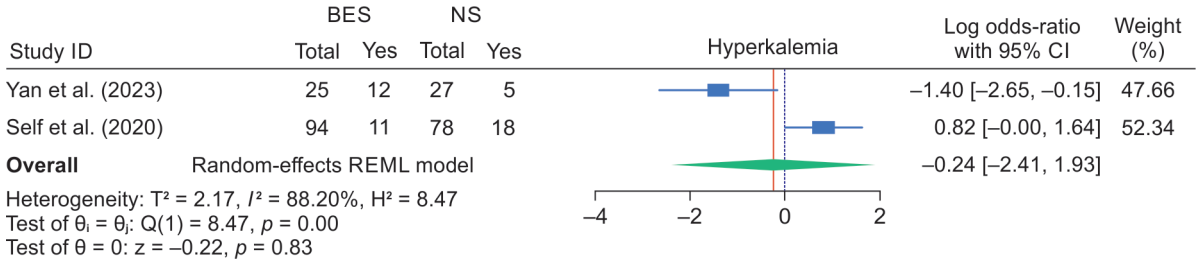

BES
NS
Study ID
Total
Yes
Total
Yes
Hyperkalemia
Log odds-ratio with 95% CI
Weight (%)
Yan et al. (2023) 25 12 27 5 –1.40 [–2.65, –0.15] 47.66
Self et al. (2020) 94 11 78 18 0.82 [–0.00, 1.64] 52.34
Overall Random-effects REML model –0.24 [–2.41, 1.93]
Heterogeneity: T² = 2.17, I² = 88.20%, H² = 8.47
Test of θi = θj: Q(1) = 8.47, p = 0.00
Test of θ = 0: z = –0.22, p = 0.83
–4
–2
0
2

Fig. 7: Forest plot of hyperkalemia

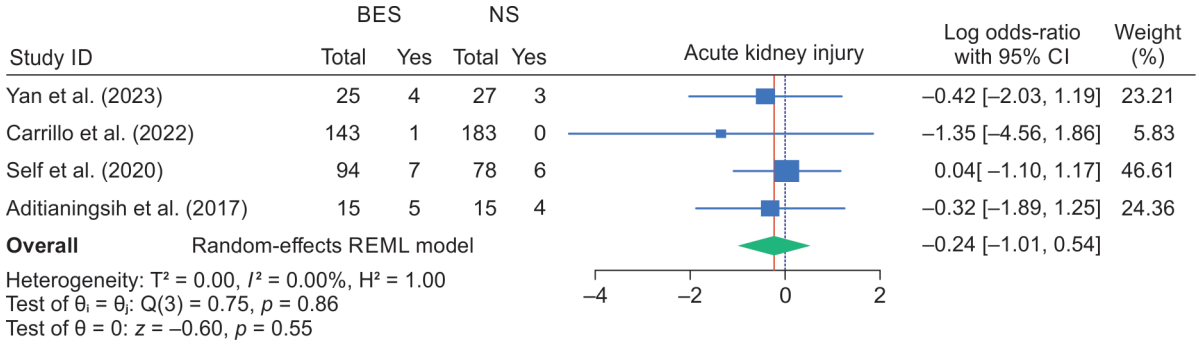

BES
NS
Study ID
Total
Yes
Total
Yes
Acute kidney injury
Log odds-ratio with 95% CI
Weight (%)
Yan et al. (2023) 25 4 27 3 –0.42 [–2.03, 1.19] 23.21
Carrillo et al. (2022) 143 1 183 0 –1.35 [–4.56, 1.86] 5.83
Self et al. (2020) 94 7 78 6 0.04[–1.10, 1.17] 46.61
Aditianingsih et al. (2017) 15 5 15 4 –0.32 [–1.89, 1.25] 24.36
Overall Random-effects REML model –0.24 [–1.01, 0.54]
Heterogeneity: T² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(3) = 0.75, p = 0.86
Test of θ = 0: z = –0.60, p = 0.55
–4
–2
0
2

Fig. 8: Forest plot of acute kidney injury

Our study found that BES caused higher bicarbonate levels and significantly lower serum chloride levels and post-resuscitation. These findings are consistent with previous research, which has shown increased metabolic abnormalities with high-volume NS administration.[37,38] Other meta-analyses, including those by Alghamdi et al., Liu et al., and Tamzil et al., have similarly reported significantly lower post-resuscitation chloride concentrations in patients treated with BES compared to NS.[15,24,25]

These findings suggest that using BES for resuscitation is likely to decrease the risk of hyperchloremia in patients with DKA,

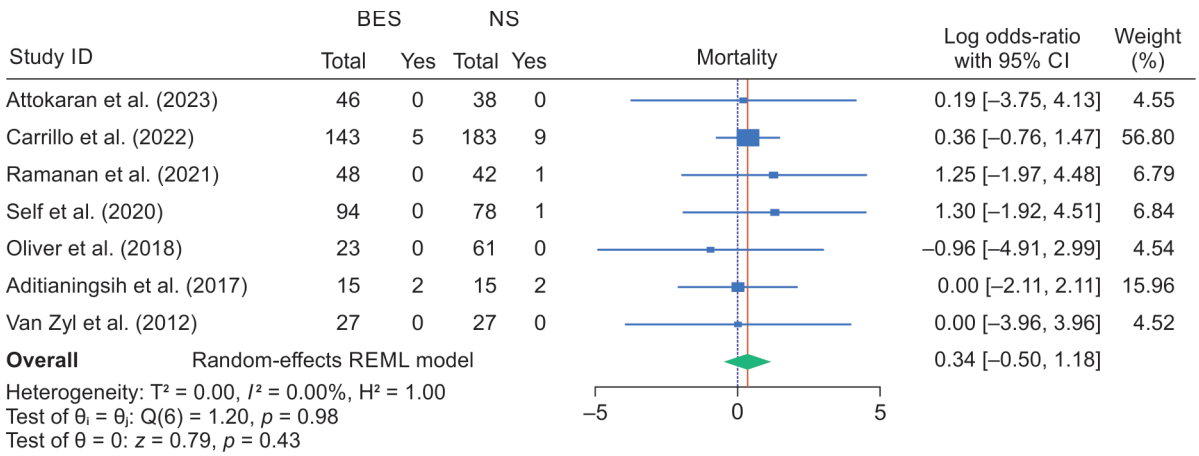

BES
NS
Study ID
Total
Yes
Total
Yes
Mortality
Log odds-ratio with 95% CI
Weight (%)
Attokaran et al. (2023) 46 0 38 0 0.19 [–3.75, 4.13] 4.55
Carrillo et al. (2022) 143 5 183 9 0.36 [–0.76, 1.47] 56.80
Ramanan et al. (2021) 48 0 42 1 1.25 [–1.97, 4.48] 6.79
Self et al. (2020) 94 0 78 1 1.30 [–1.92, 4.51] 6.84
Oliver et al. (2018) 23 0 61 0 –0.96 [–4.91, 2.99] 4.54
Aditianingsih et al. (2017) 15 2 15 2 0.00 [–2.11, 2.11] 15.96
Van Zyl et al. (2012) 27 0 27 0 0.00 [–3.96, 3.96] 4.52
Overall Random-effects REML model 0.34 [–0.50, 1.18]
Heterogeneity: T² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(6) = 1.20, p = 0.98
Test of θ = 0: z = 0.79, p = 0.43
–5
0
5

Fig. 9: Forest plot of mortality

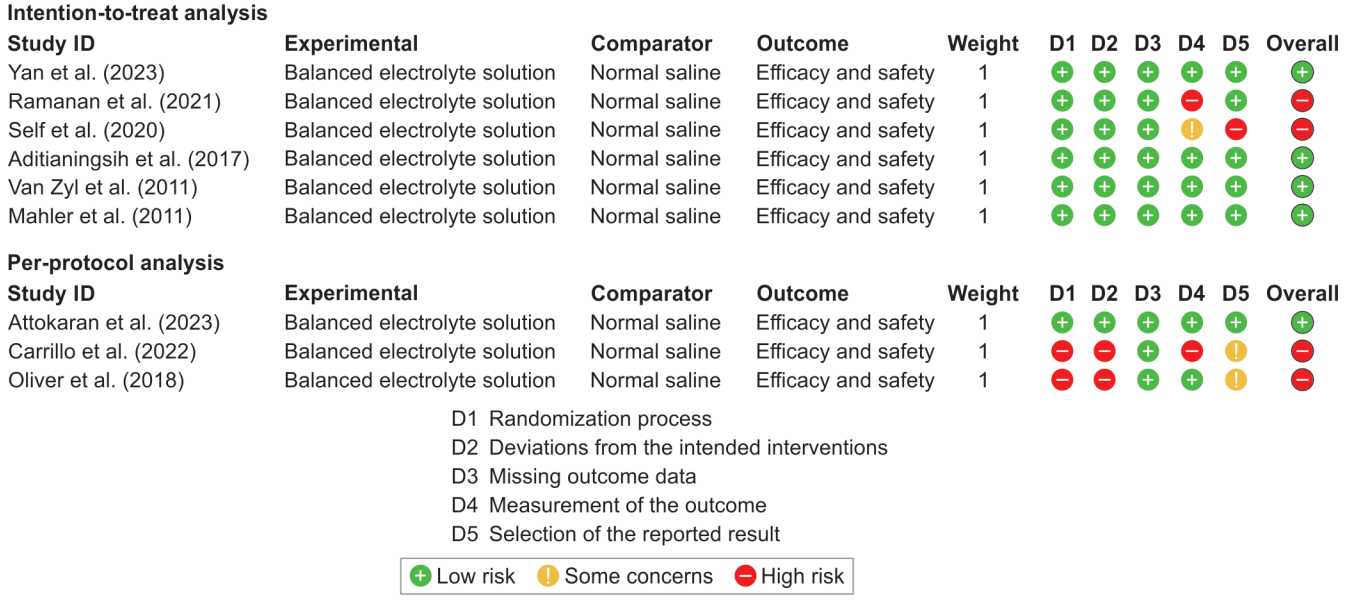

Intention-to-treat analysis
Study ID | Experimental | Comparator | Outcome | Weight | D1 | D2 | D3 | D4 | D5 | Overall
Yan et al. (2023) | Balanced electrolyte solution | Normal saline | Efficacy and safety | 1
Ramanan et al. (2021) | Balanced electrolyte solution | Normal saline | Efficacy and safety | 1
Self et al. (2020) | Balanced electrolyte solution | Normal saline | Efficacy and safety | 1
Aditianingsih et al. (2017) | Balanced electrolyte solution | Normal saline | Efficacy and safety | 1
Van Zyl et al. (2011) | Balanced electrolyte solution | Normal saline | Efficacy and safety | 1
Mahler et al. (2011) | Balanced electrolyte solution | Normal saline | Efficacy and safety | 1
Per-protocol analysis
Study ID | Experimental | Comparator | Outcome | Weight | D1 | D2 | D3 | D4 | D5 | Overall
Attokaran et al. (2023) | Balanced electrolyte solution | Normal saline | Efficacy and safety | 1
Carrillo et al. (2022) | Balanced electrolyte solution | Normal saline | Efficacy and safety | 1
Oliver et al. (2018) | Balanced electrolyte solution | Normal saline | Efficacy and safety | 1
D1 Randomization process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result
Low risk
Some concerns
High risk

Fig. 10: Risk of bias assessed with the Cochrane ROB 2 tool

consistent with their lower chloride content and similarity to plasma electrolyte composition. In contrast, higher chloride levels in NS could increase hyperchloremia risk, potentially exacerbating metabolic acidosis and increasing the likelihood of AKI.[39] Previous studies have linked hyperchloremia to metabolic acidosis, AKI, and reduced smooth muscle contractility, all of which can prolong critical illness.[17,22,40,41]

Complications from fluid therapy are likely underreported. In the current meta-analysis, complications were found to be relatively infrequent and similar across fluid types. In our study, no significant differences in AEs, including hypokalemia, hyperkalemia, AKI, or mortality, were observed. These results are in line with those of Liu et al. and Tamzil et al., who also found no significant differences in major adverse renal events, hypokalemia, or mortality between the two types of fluids.[15,24] However, an important consideration is the volume of fluid infused, which was missing in the included studies. In a recent post-hoc analysis of a large multicentric RCT comparing BES and NS, lower mortality was found with BES in patients with a volume of fluid infused >4L and in a subgroup of patients with sepsis.[42] Hence, in patients requiring large volumes of volume resuscitation, NS administration could potentially increase the risk of harm.[43]

While there were no significant differences in the primary clinical outcomes between NS and BES groups in our study, BES offers advantages in maintaining a more balanced post-resuscitation electrolyte profile, potentially mitigating the risks associated with hyperchloremia. Given the current findings and the relatively infrequent occurrence of severe adverse events, both NS and BES remain viable options for resuscitation in DKA patients. However, the choice of resuscitation fluid should be individualized, considering patient-specific factors, the volume of fluid infused, and clinical context.

Study Limitations

This study has some limitations. Firstly, the included RCTs were generally small in scale, leading to some imprecision in the pooled data, which may affect the overall certainty of our findings. Secondly, the number of RCTs that met all predefined inclusion and exclusion criteria was limited, along with heterogeneity due to factors like differences in characteristics of study participants and different

criteria used to define DKA resolution. Thirdly, we observed across all the included studies wide variations in the number of reported adverse events. Finally, despite an extensive search strategy, our review was limited to English-language literature.

Conclusion

Our study showed no significant differences between BES and NS in the time to DKA resolution or hospital stay duration, with fluid choice not affecting AEs such as hypokalemia, hyperkalemia, AKI, and mortality. BES, however, provided a better post-resuscitation electrolyte balance, featuring lower chloride and higher bicarbonate levels, which may help prevent hyperchloremic metabolic acidosis. Although both BES and NS are similarly effective and safe for resuscitation in DKA patients, BES's impact on electrolyte balance should guide fluid selection, tailored to patient characteristics and clinical context.

Clinical Significance

This study provides important insights into the choice of resuscitation fluids for managing DKA in adult patients. While both BES and NS were found to be similarly effective in terms of time to DKA resolution and hospital stay duration, BES demonstrated a superior post-resuscitation electrolyte balance, particularly by reducing chloride levels and preventing hyperchloremic metabolic acidosis. These findings suggest that BES may offer biochemical advantages, which could be crucial in optimizing patient outcomes, especially in cases where electrolyte imbalances are a concern.

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